

PB91-161604

Ambient Water Quality Criteria Document  
Addendum for Benzidene

(U.S.) Environmental Protection Agency, Cincinnati, OH

May 89



U.S. Department of Commerce  
National Technical Information Service

**NTIS**



United States  
Environmental Protection  
Agency

FIRST DRAFT  
ECAO-CIN-621  
May, 1989

# Research and Development

2891-161604

AMBIENT WATER QUALITY CRITERIA DOCUMENT  
ADDENDUM FOR BENZIDENE

## Prepared for

OFFICE OF WATER REGULATIONS  
AND STANDARDS

## Prepared by

Environmental Criteria and Assessment Office  
Office of Health and Environmental Assessment  
U.S. Environmental Protection Agency  
Cincinnati, OH 45268

DRAFT: DO NOT CITE OR QUOTE

REPRODUCED BY  
U.S. DEPARTMENT OF COMMERCE  
NATIONAL TECHNICAL  
INFORMATION SERVICE  
SPRINGFIELD, VA 22161

### NOTICE

This document is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical accuracy and policy implications.

| REPORT DOCUMENTATION PAGE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                             |                                                            | Form Approved<br>OMB No 0704-0188               |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------|--|
| <small>This reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Avenue, Washington, DC 20540, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.</small> |                                                             |                                                            |                                                 |  |
| 1. PB91-161604                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 2. REPORT DATE<br>September, 1988                           | 3. REPORT TYPE AND DATES COVERED                           |                                                 |  |
| 4. TITLE AND SUBTITLE<br>Ambient Water Quality Criteria Document Addendum for Benzidine.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                             | 5. FUNDING NUMBERS                                         |                                                 |  |
| 6. AUTHOR(S)<br>Criteria Branch/Office of Water Regulations & Standards                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                             | 8. PERFORMING ORGANIZATION<br>REPORT NUMBER                |                                                 |  |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br>U.S. EPA/Office of Water Regulations & Standards<br>Criteria Branch (WH-585)<br>401 M Street SW<br>Washington, D.C. 20460                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                             | 10. SPONSORING/MONITORING<br>AGENCY REPORT NUMBER          |                                                 |  |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                             |                                                            |                                                 |  |
| 11. SUPPLEMENTARY NOTES<br>Addendum to PB 81-117343                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                             |                                                            |                                                 |  |
| 12a. DISTRIBUTION/AVAILABILITY STATEMENT<br>Distribution unlimited                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                             | 12b. DISTRIBUTION CODE                                     |                                                 |  |
| 13. ABSTRACT (Maximum 200 words)<br>Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Benzidine.                                                                   |                                                             |                                                            |                                                 |  |
| 14. SUBJECT TERMS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                             | 15. NUMBER OF PAGES<br>16                                  |                                                 |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                             | 16. PRICE CODE                                             |                                                 |  |
| 17. SECURITY CLASSIFICATION<br>OF REPORT<br>unclassified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 18. SECURITY CLASSIFICATION<br>OF THIS PAGE<br>unclassified | 19. SECURITY CLASSIFICATION<br>OF ABSTRACT<br>unclassified | 20. LIMITATION OF ABSTRACT<br>unlimited release |  |

# DISCLAIMER

This report is an external draft for review purposes only and does not constitute Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

## TABLE OF CONTENTS

|                                            | <u>Page</u> |
|--------------------------------------------|-------------|
| INTRODUCTION . . . . .                     | 1           |
| REVIEW OF NEW DATA . . . . .               | 4           |
| Toxicologic/Carcinogenic Effects . . . . . | 4           |
| Bioconcentration Factor (BCF). . . . .     | 5           |
| QUANTIFICATION OF EFFECTS. . . . .         | 6           |
| EXISTING STANDARDS AND CRITERIA. . . . .   | 8           |
| REFERENCES . . . . .                       | 9           |

## LIST OF ABBREVIATIONS

|       |                                                  |
|-------|--------------------------------------------------|
| BCF   | Bioconcentration factor                          |
| CRAVE | Carcinogen Risk Assessment Verification Endeavor |
| LOAEL | Lowest-observed-adverse-effect level             |
| ppm   | Parts per million                                |
| RfD   | Reference dose                                   |
| RQ    | Reportable quantity                              |
| TLV   | Threshold limit value                            |

## INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods, if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{NOAEL \text{ or } LOAEL}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (Inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on benzidine, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

## REVIEW OF NEW DATA

### Toxicologic/Carcinogenic Effects

Epidemiologic evidence linking benzidine exposure to bladder cancer is sufficient to classify benzidine in Group A - human carcinogen (U.S. EPA, 1986b). In an epidemiologic study, Zavan et al. (1973) identified 11 cases of bladder cancer in 25 workers exposed to 0.005-17.6 mg/m<sup>3</sup> for a mean period of 11.46 years. This same chemical plant was also among those identified as having a positive association in a case-control study of male bladder cancer mortality using commercial city directories for data on employment history (Steenland et al., 1987).

A 30-year follow-up study of workers at a benzidine manufacturing plant in Connecticut found a statistically significant excess incidence of bladder cancer in male workers (Meigs et al., 1986). Exposure was estimated as high ( $\geq 2$  years), medium (6 months-2 years), low (2 days-6 months) and none (0-2 days), but no quantitative estimates of dosages were given. Among 830 males, 48 first primary cancers were found including 8 bladder cancer cases. Benzidine exposure was involved in 7 (6 high and 1 medium exposure) of the 8 cases of bladder cancer. The overall excess bladder cancer incidences were statistically significant (8 observed vs. 2.3 expected, standard incidence ratio of 343,  $p < 0.01$ ). Analysis of risk by the exposure levels revealed that significant elevation of bladder tumors was limited to the highest level of benzidine exposure (standard incidence ratio of 1303). No significantly elevated risk was found for cancers at other anatomical sites in men or at any anatomical site in women. No pattern of increasing risk was observed with increasing benzidine exposure for sites other than the bladder.

Benzidine is also carcinogenic via the oral, subcutaneous and intraperitoneal routes of exposure to a variety of mammalian species, with a multiplicity of target organs. These studies are discussed in detail in U.S. EPA (1980, 1986a). Studies in which rodents were exposed to benzidine in drinking water also provide quantitative data on lung and liver carcinogenicity (Littlefield et al., 1983, 1984; Frith et al., 1979, 1980). Several dose levels ( $\geq 20$  ppm) were used for up to 33 months. These data were reviewed by U.S. EPA (1986a) and were considered less appropriate than the epidemiologic data as the basis for quantitative risk assessment. This assessment (U.S. EPA, 1986a) is part of the documentation for the verified slope factor for oral exposure (U.S. EPA, 1986b) (see following section).

#### Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for benzidine is currently undergoing agency review. The BCF value of 87.5 determined in U.S. EPA (1980) will be used until the review of the new information is completed.

### QUANTIFICATION OF EFFECTS

Ambient water quality criteria of  $1.2 \times 10^{-3}$ ,  $1.2 \times 10^{-4}$  and  $1.2 \times 10^{-5}$   $\mu\text{g/l}$  corresponding to lifetime increased cancer risk levels of  $10^{-2}$ ,  $10^{-3}$  and  $10^{-5}$ , respectively, were derived for benzidine (U.S. EPA, 1980) using data from the epidemiological study of Zvon et al. (1973). In this study, 25 manufacturing plant workers exposed mainly to benzidine in ambient air containing 0.005-17.6  $\text{mg/m}^3$  for a mean period of 11.46 years. Of the 25, 11 developed bladder cancer, while 2 others had benign bladder tumors.

The derivation of criteria assumed a 70 kg body weight and a daily intake of 2 l water and 6.5 g fish and shellfish with a BCF of 87.5 (a value derived for an average lipid content of 3%), and were extrapolated from epidemiological data of Zvon et al. (1973) using a one-hit model with a time factor. All incidences of tumors including two benign tumors (13 cases), rather than bladder cancer alone (11 cases), were used. Estimation of dose level was based on the average urine level of benzidine at the end of the workshift ( $\sim 0.04 \text{ mg/l}$ ) as reported by Zvon et al. (1973), and on the assumption that the daily urinary output of 1.2 l/day contained 1.45% of the total dose (Rinde and Troll, 1974). Other variables used in the extrapolation were the average duration of exposure of 11.46 years and the average age of 56.5 years for the cohort at the end of the study (Zvon et al., 1973); an average of 240 working days in a year; and the United States life expectancy of 71.3 years (U.S. EPA, 1980).

Dose was obtained by:

$$d = [(0.04 \times 1.2)/70] \times 240/365 \times 11.46/56.5 = 0.0063 \text{ mg/kg/day}$$

Using the model:  $P = 1 - [-Bdt^2]$ , B was calculated as:

$$B = [-\ln(1 - 13/25)]/[0.0063 \times (56.5/71.3)^2] = 234.13 \text{ (mg/kg/day)}^{-1}$$

Therefore, the water concentration corresponding to the  $10^{-5}$  risk level for lifetime exposure was calculated as:

$$C = [70 \times 10^{-5}]/[234.13 \times (2 + 0.0065 \times 87.5)] = 1.16 \text{ ng/L}$$

Similar concentrations for the  $10^{-6}$  and  $10^{-7}$  risk levels were  $1.16 \times 10^{-1}$  and  $1.16 \times 10^{-2}$  ng/L, respectively.

The oral slope factor of  $2.3 \times 10^2 \text{ (mg/kg/day)}^{-1}$  as derived in the preceding paragraph has been verified by the EPA Agency-wide CRAVE committee and is available on IRIS (U.S. EPA, 1986b). Based on the verified slope factor, ambient water criteria for benzidine remain as derived in the 1980 AWQCD (U.S. EPA, 1980).

| Exposure Assumptions<br>(per day)                                          | Risk Levels and Corresponding Criteria ( $\mu\text{g/L}$ ) |                      |                      |                      |                      |
|----------------------------------------------------------------------------|------------------------------------------------------------|----------------------|----------------------|----------------------|----------------------|
|                                                                            | 0                                                          | $10^{-7}$            | $10^{-6}$            | $10^{-5}$            | $10^{-4}$            |
| 2 L of drinking water<br>and consumption of 6.5 g<br>of fish and shellfish | 0                                                          | $1.2 \times 10^{-5}$ | $1.2 \times 10^{-4}$ | $1.2 \times 10^{-3}$ | $1.2 \times 10^{-2}$ |
| Consumption of fish and<br>shellfish only                                  | 0                                                          | $5.3 \times 10^{-5}$ | $5.3 \times 10^{-4}$ | $5.3 \times 10^{-3}$ | $5.3 \times 10^{-2}$ |

The slope factor has considerable uncertainty associated with its derivation because of the very small cohort in the epidemiologic study, lack of smoking history and assumptions that may not be valid, including use of inhalation data for oral risk estimate. In addition, the 1.45% urinary recovery factor based on a study of monkeys (Rinde and Troll, 1975) may change significantly because of methodological problems and differences in exposures between monkeys and humans exposed in occupational settings. Even with this caveat, however, the human data are preferred because of the uniqueness of the bladder as the specific human target organ not sensitive in animal models.

### EXISTING STANDARDS AND CRITERIA

The U.S. EPA (1987) verified an RfD of 0.002 mg/kg/day based on a LOAEL of 1.8 mg/kg/day in mice for brain cell vacuolization and liver cell alterations from a chronic drinking water bioassay (Littlefield et al., 1983) and using an uncertainty factor of 1000.

The inhalation slope factor of  $2.3 \times 10^2 \text{ (mg/kg/day)}^{-1}$ , based on the data of Zavan et al. (1973), has been verified by the EPA Agency-wide CRAVE committee and is available on IRIS (U.S. EPA, 1986b).

An RQ of 1 pound has been proposed, based upon the potential carcinogenicity of benzidine (potency group 1 and the weight of evidence designation of Group A), and is available on IRIS (U.S. EPA, 1988).

ACGIH (1987) recommended virtual elimination of exposure to benzidine and has classified benzidine in category A1 (confirmed human carcinogens) without a TLV.

## REFERENCES

ACGIH. (American Conference of Governmental Industrial Hygienists). 1987. TLVs - Threshold Limit Values and Biological Exposure Indices for 1987-1988. Cincinnati, OH. p. 12, 41-42.

Frith, C.H., K.P. Baetcke, C.J. Nelson and G. Schieferstein. 1979. Importance of the mouse liver tumor in carcinogenesis bioassay studies using benzidine dihydrochloride as a mode. Toxicol. Lett. 4(6): 507-518.

Frith, C.H., K.P. Baetcke, C.J. Nelson and G. Schieferstein. 1980. Sequential morphogenesis of liver tumors in mice given benzidine dihydrochloride. Eur. J. Cancer. 16: 1205-1216.

Littlefield, N.A., C.J. Nelson and C.H. Frith. 1983. Benzidine dihydrochloride: Toxicological assessment in mice during chronic exposures. J. Toxicol. Environ. Health. 12(4-6): 671-685.

Littlefield, N.A., C.J. Nelson and D.W. Gaylor. 1984. Benzidine dihydrochloride: Risk assessment. Fund. Appl. Toxicol. 4(1): 69-80.

Meigs, J.W., L.D. Marret, F.J. Ulrich and J.T. Flannery. 1986. Bladder tumor incidence among workers exposed to benzidine: A 30-year follow-up. J. Natl. Cancer Inst. 76: 1-8.

Rinde, E. and W. Troll. 1974. Azo dyes as potential bladder carcinogens. Proc. Am. Assoc. Cancer Res. 15: 65. (Meeting Abstr.) (Cited in U.S. EPA, 1980)

Rinde, E. and W. Troll. 1975. Metabolic reduction of benzidine azo dyes to benzidine in the rhesus monkey. J. Natl. Cancer Inst. 55: 181.

Steenland, K., C. Burnett and A.M. Osorio. 1987. A case-control study of bladder cancer using city directories as a source of occupational data. Am. J. Epidemiol. 126: 247-257.

U.S. EPA. 1980. Ambient Water Quality Criteria for Benzidine. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-023. NTIS PB81-117343.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Benzidine. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/X-86/157. NTIS PB88-219431/AS.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Carcinogenicity Assessment for Lifetime Exposure to Benzidine. Online. (Verification date 12/17/86) Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1987. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Benzidine. Online: Input pending. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1988. Integrated Risk Information System (IRIS). Chemical File for Benzidine. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Zavon, M.R., U. Hoegg and E. Bingham. 1973. Benzidine exposure as a cause of bladder tumors. Arch. Environ. Health. 27: 1-7.